REMARKS

Claims 77-101 are pending in this application. Claims 77-101 were previously indicated as allowable and this application was withdrawn from issue by the Office after payment of the issue fee. Applicants note with appreciation that the Office will hold the issue fee and apply it to any subsequent issue fee due in this case or refund the full amount upon Applicants' request.

Applicants note with appreciation the summary of the case and issues set forth in the opening paragraphs of the Action. The summary, however, does not accurately reflect the November 20, 2003 Examiner's Amendment accompanying the Notice of Allowance. By that amendment, claims 102-106 were cancelled without prejudice and without disclaimer of the subject matter contained therein, and claims 83 and 99 were amended. The above Listing of Claims reflects these previously presented amendments, in a clean format since the amendments were previously presented.

35 U.S.C. § 101/112

Claims 77-106 stand rejected for allegedly lacking support by "either a specific and substantial asserted utility or a well established utility." The rejection was maintained for reasons of record in the March 21, 2003 Office Action.

The rejection was originally overcome through a response that contained, in part, data corroborating that hARE-2 functions as a GPCR to modulate the level of cAMP or IP_3, as taught in the application as filed. Applicants note with appreciation the Examiner's helpful suggestion, offered during several conversations with attorney Michael A. Patané, to incorporate this previously presented data into a continuation-in-part application. Applicants further note with appreciation the examiner's indication that doing so would overcome the rejection and bring

about an allowance. Applicants, however, continue to believe that it is entitled to the priority date of the original application because a specific, substantial, and credible utility would have been apparent to those of skill in the art at the time of filing.

hARE-2 as a GPCR

In this application, the Action appears to decide the utility question in large part on whether hARE-2 is, or can be, characterized as a GPCR. The prior action, in setting forth the utility rejection, stated on page 5, lines 17-20:

> Therefore, there is little doubt that, after further characterization, the protein encoded by the claimed nucleic acid is found to be a member of the GPCR family, the claimed protein would have a specific, substantial, and credible utility.

Applicants have always maintained their position that hARE-2 is a GPCR. Nothing in the specification suggests that hARE-2 is anything other than a GPCR.

Nonetheless, the Action again asserts the belief that the receptor in question, hARE-2, is not recognized as a GPCR by Applicants' specification. Indeed, here the Action states:

> Applicants have traversed this rejection on the premise that the disclosure of the ***probable*** fact that a hARE-2 protein of the instant invention functions as a G protein-coupled receptor protein in the substantia nigra is sufficient for utility. (Emphasis added)

It is unclear whether "probable" refers to the fact that hARE-2 functions as a GPCR or that it is expressed in the substantia nigra or both. Applicants, however, have not left either fact open to debate. Applicants repeatedly identify and refer to hARE-2 as a GPCR, when discussed alone or along with other GPCRs throughout the original specification and claims. This fact is recognized by the Action, which states "The only disclosed function for a protein of the instant

invention in the application as filed, however, is as a GPCR protein." Thus, even the Action appears to recognize the fact that Applicants have asserted hARE-2 is a GPCR. Similarly, the specification clearly indicates that hARE-2 is expressed in the substantia nigra, as recognized by the Action which states "Table C, page 27 of the specification discloses that hARE-2 is expressed in the left and right cerebellum and in the substantia nigra." Thus, by the Action's own words, the specification clearly asserts that hARE-2 is a GPCR ***and*** is expressed in the substantia nigra. The Action provides no evidence of any reason to doubt these assertions.

It would be readily apparent to a person skilled in the art from the technical knowledge available at least as early as the priority date that hARE-2 is a G protein-coupled receptor (GPCR). In questioning whether hARE-2 is a GPCR, the Action acknowledges that Table A, page 8 of the specification discloses that hARE-2 has 53% homology to GPR27. The Action alleges that the specification fails to disclose whether this homology is random, stretches of homology, or pockets of homology and whether the homology is in conserved or non-conserved areas. The Examiner also states that Applicants have failed to show the 7 hydrophobic transmembrane domains that are characteristic and highly conserved in GPCRs or alignments of hARE-2 with GPR27.

Applicants respectfully point out that they have provided an alignment of hARE-2 with GPR27 as Figure 1 of priority provisional application US 60/136,436, where it was shown that the homology between hARE-2 and GPR27 is observed over the entire length of hARE-2. Applicants also respectfully point out that a person of skill in the art at least as early as the priority date of the application would readily have appreciated that hARE-2 is characterized by

the 7 hydrophobic domains characteristic and highly conserved in GPCRs as well as by additional conserved features of GPCRs.

It was well known to the skilled artisan that GPCRs are characterized by seven transmembrane (membrane spanning) domains, designated TM-1 to TM-7 (*see, e.g.,* page 1 paragraph [0004] of the application as filed; and page 2, left column, lines 13-27, Figure 2, and Figure 3 of Probst et al. (1992) DNA Cell Biol., 11:1-20). It was well known to the skilled artisan that TM-6 is characterized by a tryptophan residue and a proline residue conserved in many GPCRs (*see, e.g.,* page 3, lines 3-6 of paragraph [0031] of the application as filed; and page 2, left column, lines 32-40, to right column, lines 1-5, Figure 2, and Figure 3 of Probst et al.) It was well known to the skilled artisan that GPCRs are characterized by a highly conserved arginine residue at the intracellular end of TM3, typically as part of a perfect or imperfect "DRY" motif (*see, e.g.,* page 12, left column, lines 30-34, Figure 2, and Figure 3 of Probst et al.)

Methods of predicting the location of the transmembrane domains of a GPCR based on the sequence were available at least as early as the priority date of the application. One such method is TMHMM (transmembrane hidden Markov model), which is described in: Sonnhammer et al. (1998) In J Glasgow et al., eds, Proc Sixth Int. Conf. on Intelligent Systems for Molecular Biology, 175-182, enclosed. In order to demonstrate to the Examiner that known methods could have been applied by those skilled in the art to identify TM-1 to TM-7, the conserved tryptophan and proline residues in TM-6, and the highly conserved arginine residue at the intracellular end of TM3, Applicants have applied the TMHMM method to SEQ ID NO:20 (hARE-2 amino acid sequence). The result is shown in **Annex 1**.

Annex 1 shows that hARE-2 is predicted to have seven transmembrane regions, as expected for a GPCR. **Annex 1** shows that TM-6 is predicted to correspond to amino acids 289-311 of SEQ ID NO:20. This predicted amino acid sequence for TM-6, shown in **Annex 2,** contains a tryptophan residue (amino acid position 299) and a proline residue (amino acid position 301), consistent with the tryptophan and proline residues which are conserved in TM-6 of many GPCRs. The highly conserved arginine residue adjacent to TM3 in the second can be found at amino acid position 121. It follows that it would be readily apparent to a person skilled in the art at least as early as the priority date that hARE-2 is a GPCR. The Office has provided no countervailing evidence to dispute this fact.

In further support of its position, the Action states on page 5, lines 8-10, of the Office Action:

> In any event, the ligand for the claimed hARE-2 protein is unknown, no GTPase assay has been provided, no stimulation of GTPase has been demonstrated in membranes of hARE-2 transfected cells investigating GTPase activity.

However, the fact that hARE-2 is a GPCR would have been apparent to those skilled in the art even absent a GTPase assay as evidenced by Probst et al., in which GPTase activity is not mentioned.

The Action states that Applicants cannot rely on Graph 1 to establish the utility of hARE-2, because the graph was provided after the application filing date in Applicants' response dated 19 September 2003. Applicants respectfully assert, as was asserted previously in Applicants' 19 September 2003 response, that Graph 1 is not provided to establish utility for hARE-2 as a GPCR, but rather to corroborate the asserted and well-established utilities for hARE-2 as a

GPCR. Applicants respectfully submit that the data in Graph 1 simply provide further exemplification and confirmation of the invention, exemplification and confirmation of the disclosure in the application as filed of hARE-2 GPCR as modulating the intracellular level of cAMP or IP_3.

With respect to the Examiner's questions relating to Graph 1, wherein hARE-2 is shown to be constitutively active and to reduce the level of intracellular cAMP, Applicants appreciate the opportunity to provide the following clarifications:

- The amount of plasmid DNA is held constant in the transfections. For example, for the "pCMV" (negative control) sample, 4 μg pCMV was used for transfection. For the "pCMV/TSHR" sample, 2 μg pCMV was co-transfected with 2 μg pCMV containing TSHR.

- The open histograms wherein the activity was evidenced in the absence of TSH shows that hARE-2 is constitutively active and reduces the level of intracellular cAMP independently of binding TSH.

- The experiment was carried out with groups of cells, as would be understood by one of skill in the art and as taught in Example 2 of the application as filed.

- Applicants respectfully submit that speculation as to whether Ca^{2+} is an hARE-2 second messenger which inhibits cAMP release is irrelevant because *both* an elevation of intracellular Ca^{2+} and a reduction of intracellular cAMP have been shown to adversely affect viability of neurons of the substantia nigra; see Hulley et al. and Hirsch et al. Applicants respectfully submit that Graph 1 simply exemplifies and confirms the disclosed utility of hARE-2 for screening for

agents which influence substantia nigra function useful as pharmaceutical agents for a disease or disorder related to the substantia nigra. The skilled artisan would be aware of such diseases or disorders, for example Parkinson's disease. The skilled artisan would appreciate from Graph 1 that, e.g., an inverse agonist or an antagonist of hARE-2 would promote the viability of neurons of the substantia nigra and thereby be useful in Parkinson's disease, whether or not the reduction in cAMP in Graph 1 was preceded by an elevation of intracellular Ca^{2+} [see, Hulley et al. and Hirsch et al.]. The skilled artisan at least as early as the priority date of the application would be able to identify an agent screened for influencing substantia nigra function as an agent useful in promoting viability of neurons of the substantia nigra, using for example the assays taught by Hulley et al. and Hirsch et al.

Applicants appreciate the opportunity to clarify here that the reduction of the level of intracellular cAMP is consistent with hARE-2GPCR coupling, for example, to Gi (see, e.g., paragraphs [0034] to [0042] on pages 3-4 of the application as filed.)

Applicants respectfully submit that the skilled artisan, at least as early as the priority date, would have had no reason to doubt that hARE-2 is a GPCR for at least the reasons discussed above, and that the utility of hARE-2 does not need to rely on a demonstration of GTPase activity and that compounds screened against hARE-2 can be used to treat diseases or disorders of the substantia nigra, such as Parkinson's disease.

According to MPEP § 2107.02, the Office must presume the utility set forth by Applicants is sufficient absent evidence of a reason to suspect otherwise. The MPEP states:

> *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. See *In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

The burden is upon the Office to provide evidence showing a reason to question Applicants' statements of utility. MPEP § 2107.02 continues to provide guidance in stating:

> in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. * * * This means that if the applicant has presented facts that support the countervailing facts and reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false).

Thus, to establish lack of utility, the Office must provide evidence to contravene Applicants' statement of utility such that it is more likely than not that Applicants' assertion is false. Here, the Action appears to cast doubt as to whether hARE-2 is a GPCR, despite Applicants' repeated reference to hARE-2 as a GPCR. The Action even goes so far as to point out that the specification does not present an evaluation of hARE-2 with respect to the characteristics of GPCRs set forth in the Background. Applicants, however, need not set forth such an evaluation where it has clearly set forth that hARE-2 is a GPCR. The burden is on the Office to provide evidence showing a reason to question Applicants' assertion. The Action, however, does not point to any "countervailing facts and reasoning sufficient to establish that a

person of ordinary skill would not believe" Applicants' characterization of hARE-2 as a GPCR. Indeed, the Office cannot point to any such evidence, because, as the previously submitted data confirms, with techniques available at the time of filing, one of skill in the art could readily confirm that hARE-2 is a GPCR.

Those of skill in the art, at the time of filing, would not have had reason to question Applicants' characterization of hARE-2 as a GPCR. Those of skill in the art would have been satisfied with Applicants' conclusion that hARE-2 is a GPCR in recognition of the various characteristics of GPCRs and the descriptions set forth in the specification. In fact, those skilled in the art would have been aware of several means, including the testing and results provided previously, and reattached hereto, to verify Applicants' assertion. (see Graph 1.) Ultimately, had one questioned the fact that hARE-2 is a GPCR, test results would have readily laid those questions to rest.

The Action simply does not, and cannot, provide evidence that suggests that it is more likely than not that the statement of the Applicants is false. Accordingly, Applicants' assertion that hARE-2 is a GPCR ***must*** be accepted by the Office. Given this fact, it logically follows that there can be "little doubt" as to the utility of the claimed protein.

Even so, Applicants need not rely on the characterization of hARE-2 as a GPCR for utility purposes, because those of skill in the art would immediately recognize the usefulness of the invention and the application sets forth a specific, substantial, and credible utility.

Those of Skill in the Art Would Have Immediately Appreciated Why the Invention is Useful

At least as early as the time of filing, a person of ordinary skill in the art would have immediately appreciated why the invention is useful. Those of skill in the art, e.g. biochemists

and molecular biologists, would have immediately appreciated that the claimed invention directed to the receptor hARE-2 could have been used, for example, in an assay to identify a ligand that would have been useful to treat a disease or disorder of the substantia nigra such as Parkinson's disease. Those of skill in the art would have immediately appreciated that the claimed invention directed to the receptor hARE-2 would have been useful because:

(a) it was known that hARE-2 is a GPCR that is selectively expressed in the substantia nigra. See, for example, Table C of the application as filed (page 10 of US 2003/0017528 A1);[1]

(b) those of skill in the art were well aware of GPCR screening methods that could be used to screen compounds against hARE-2. Exemplary screening methods are provided, e.g., in paragraphs [0034] to [0042] on pages 3-4 of the application as filed;

(c) it was known that modulating a GPCR, such as hARE-2, can modulate the level of cAMP or IP_3 (see, e.g., paragraphs [0039] to [0042] on page 4 of the application as filed, such that modulating hARE-2 can modulate the level of cAMP or IP_3 selectively in the substantia nigra;

(d) it was known that an elevation of intracellular IP_3 can lead to an elevation of intracellular Ca^{2+} [Berridge, Nature (1993) 361:315-325];

(e) it was known that the viability of neurons in the substantia nigra is sensitive to the level of intracellular cAMP [Hulley et al., European Journal of Neuroscience (1995) 7:2431-2440] and to the level of intracellular Ca^{2+} [Hirsch et al., J Neural Transm Suppl (1997) 50:79-88];

(f) it was known that the pathological process behind the motor disabilities of Parkinsonism is a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum. Brain dopamine deficiency

[1] Identification in Table C of hARE-2 expression also in left cerebellum and right cerebellum indicates that the tissue panel used to show selective expression of hARE-2 in substantia nigra was that of the RNA Master Blot™ grid shown in Figure 1B (see, e.g., page 10 lines 14-17 of paragraph [0100]).

is sufficient to explain all of the major symptoms of Parkinson's disease [see, e.g., the final two sentences of the Abstract in Blaszczyk, Acta Neurobiol Exp (Wars.) 58:79-93].

(g) thus, one skilled in the art, upon reading Applicants' specification, would have appreciated that modulating neuron viability in the substantia nigra would have been useful for treating a disease or disorder relating to degeneration of neurons of the substantia nigra, for example, Parkinson's disease;

(h) thus, those of skill in the art would have recognized that and would have had no reason to doubt that hARE-2 could have been used in an assay to identify a ligand that would have been useful for modulating substantia nigra function to treat a disease or disorder of the substantia nigra, for example Parkinson's disease.

Thus, a person of ordinary skill in the art would have immediately appreciated that the claims directed to hARE-2 would have at least one well-established utility, because hARE-2 can be employed in screening assays to identify, for example, ligands useful for treating a disease or disorder of the substantia nigra such as Parkinson's disease.

The Utility

Applicants respectfully submit that those of skill in the art would readily recognize the utility of using the GPCR, hARE-2, in the treatment or identification of candidates for treatment of motor impairment disorders associated with the substantia nigra, such as Parkinson's disease.

The Utility is Specific

Applicants respectfully submit that the utility is specific. Each of the claims is directed specifically to hARE-2 and not to GPCRs generally. Despite the characterization in the Action, the disorders to be treated are also specific to diseases or disorders related to the substantia nigra, such as motor impairment disorders, including Parkinson's disease. The specification indicates that the localized expression data is used to determine where the receptor is expressed, and

accordingly is associated with a functionality. In this case, expression was found in the substantia nigra--an area of the brain known to be correlated to motor function and motor impairment disorders. This knowledge coupled with the knowledge that modulation of hARE-2 (e.g., by a ligand identified through a screening assay that employs hARE-2) can lead to a modulation of cAMP or IP_3 specifically in the substantia nigra, would lead those of ordinary skill in the art to recognize the identified ligand can be used specifically to treat a disease or disorder of the substantia nigra such as Parkinson's disease. Thus, the utility is specific as contemplated by 35 U.S.C. § 101.

The Utility is Substantial

The specification does not blindly recite the use of hARE-2 for treating an unknown disease or disorder, rather, the specification is clear that hARE-2 can be used to treat diseases and disorders associated with the substantia nigra, such as motor impairment diseases and disorders. The treatment of motor impairment disorders and, especially Parkinson's disease, is a real world use.

Several noteworthy celebrities have Parkinson's disease and have been outspoken in their search for a cure. In particular, in recent years, actor Michael J. Fox, who suffers from Parkinson's, has spoken before Congress, and other audiences, to raise awareness for the disease and the search for treatment and a cure. Such efforts are hardly, if ever, made for a cause lacking "real world" implications. Many people suffer from this disabling disorder and would benefit from a treatment for the disease or even a treatment preventing or limiting further exacerbation of the disease

The utility is substantial because the use of hARE-2 in an assay to identify possible ligands for treating a disease or disorder of the substantia nigra such as Parkinson's disease is a "real world" use. In this regard, Applicants note that the Revised Interim Utility Guidelines Training Material (herein after "Training Material") states that "an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use." See page 6 of the Training Material. In the present case, the ligands that can be identified in an assay employing hARE-2 have substantial utility themselves because, as disclosed by Applicants, these ligands can be administered to treat a disease or disorder of the substantia nigra, such as Parkinson's disease. Thus, the use of hARE-2 in an assay to identify ligands thereof for treating disorders of the substantia nigra also would have a "real world" use.

Thus, Applicants have disclosed a substantial, real world use as contemplated by 35 U.S.C. § 101.

The Utility is Credible

As mentioned above, it is the Office's burden to provide evidence tending to show that the utility is not credible. The Action offers no factual evidence to contravene Applicants' assertion of utility. Absent any factual evidence from the Office that would lead one to question the credibility of the utility, the Office must recognize the asserted utility. Applicants respectfully submit that all the requirements of 35 U.S.C. § 101 have been satisfied.

Those of skill in the art would have had no reason to question the use of the GPCR, hARE-2, which is expressed in the substantia nigra, to screen for ligands that could have been administered to a patient to treat a disease or disorder of the substantia nigra, such as Parkinson's disease.

The MPEP dictates that once the Applicants have provided a reason for why the claimed invention is useful, the Office personnel may maintain a rejection for alleged lack of utility *only* if the Office Action establishes that one of ordinary skill would find that the asserted utility is not credible. For example, the MPEP §2107.02 II. B. states that:

> If the applicant subsequently indicates why the invention is useful, Office personnel should review that assertion according to the standards articulated below for review of the credibility of an asserted utility.

The "standard articulated below for review of the credibility of an asserted utility" is found at MPEP §2107.02 III. B, which states:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. (Emphasis in original.)

The use of hARE-2 to screen for ligands of hARE-2, wherein such ligands can be administered to treat a disease or disorder of the substantia nigra, such as Parkinson's disease, would have been recognized by a person of ordinary skill in the art at least as early as the time of filing, upon reading Applicants' specification and claims. There is no evidence of record that would contradict the logic underlying this assertion or that would indicate that the facts upon which it is based, as set forth above, are inconsistent with the logic underlying the assertion.

Thus, Applicants respectfully assert that those of skill in the art would have immediately recognized the utility of the invention and that 35 U.S.C. § 101 is satisfied.

In view of the preceding remarks, Applicants respectfully request the rejections under 35 U.S.C. § 101 be withdrawn.

Claims 77-106 also stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, on the basis that the claims allegedly lack utility. In light of the arguments above, Applicants respectfully submit that those skilled in the art would recognize both the utility of the invention and how to use it. Moreover, methods of screening for modulators of GPCRs were well known in the art at the priority filing date of the present application, and such methods were described in the earliest priority document. See, for example, Sections D.1. and D.2. on pages 15-17 of Provisional Application 60/136,436, filed on May 28, 1999. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

In conclusion, Applicants respectfully assert that the claimed inventions directed to hARE-2 have a well-established utility, and that the Office Action has not provided any reason for one of ordinary skill in the art to doubt the credibility of such utility. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101 and § 112, first paragraph. Further, Applicants assert that the claims are in condition for allowance, and respectfully request notification to that effect.

Applicants point out that the above cited Berridge, Hulley et al., and Hirsch et al. references were previously submitted to the Office in an Information Disclosure Statement in this case. The Blaszczyk reference has been included in an Information Disclosure Statement being filed with this Response.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,
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